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Hydroxychloroquine Induced QTc Prolongation in Patients with Different Levels of COVID-19 Severity

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ABSTRACT

Objective: In the absence of large-scale studies, the extent of QT-interval prolongation during hydroxychloroquine (HY) treatment remains unclear. We aim to evaluate the extent of hydroxychloroquine induced QTc prolongation and its relation to COVID-19 severity, polymorphic ventricular arrhythmias and sudden arrhythmic deaths.

Methods: We conducted a large-scale, retrospective analysis of QT-interval prolongation in COVID-19 patients admitted between March 1, 2020, and June 1, 2020 and treated with hydroxychloroquine alone or with azithromycin (HY/AZ). 2,014 patients from 8 secondary and tertiary care hospitals with paired ECG data were included in the final analysis. We examined baseline and on-therapy QTc measurements and their relationship to clinical severity. QT-interval was corrected using Bazett and Fridericia formulas.

Results: Baseline $QTc_{(Bazett)}$ was 427.6±25.4 ms, and the longest $QTc_{(Bazett)}$ during treatment was 439.2±30.4 ms (p<0.001). Severe QTc prolongation (QTc ≥500 ms) was observed in 1.7-3.3% of patients (Fridericia and Bazett, respectively), with no recorded cases of polymorphic ventricular arrhythmia. $QTc_{(Bazett)}$ prolongation was higher in combination therapy (ΔQTc 22.2 ms vs. 11.0 ms, p<0.001) and in patients with higher clinical severity (asymptomatic: 428.4±25.4 ms, severe COVID-19 infection: 452.7±35.7 ms, p<0.001). The overall in-hospital mortality was 3.97%, and deceased patients had longer on-therapy $QTc_{(Bazett)}$ than survivors (459.8±21.4 ms vs. 438.4±29.9 ms, p<0.001).

Conclusions: The incidence of severe QTc prolongation with HY was low and not associated with ventricular arrhythmia. The safety concerns surrounding the use of HY may have been overestimated; however, caution should be exercised when using HY in patients with risk factors for QT prolongation.

Keywords: COVID-19, QT-interval, QTc, hydroxychloroquine, azithromycin

Strengths and limitations of the study:

- To date, this is the largest, multi-centre study with paired ECG data examining the effects of HY on QTc prolongation.
- The study population included patients with different clinical severity levels. Hence, the effects of HY on QTc in our study are more applicable to a wider population.
- The retrospective design of the study, the absence of a control group and the strong male preponderance are limitations to this study which was performed during the COVID-19 pandemic.
- Deceased patients or with more severe clinical infection had longer QTc interval
- The study confirms that when HY is used and monitored appropriately, it should be considered a safe drug

1 Introduction

The coronavirus disease 2019 (COVID-19) pandemic brought unprecedented diagnostic and therapeutic challenges to the world. Until a proven disease-specific treatment is available, repurposing of available drugs is amongst the few options available to reduce its mortality and morbidity.[1]

Hydroxychloroquine (HY) is a commonly used antimalarial agent frequently prescribed for rheumatoid arthritis and systemic lupus erythematosus (SLE). Azithromycin (AZ) is a macrolide antibiotic with well-described anti-inflammatory and immunomodulatory properties.[2] The antiviral efficacy of HY against SARS-CoV 2 in some in-vitro studies[3,4] along with favourable outcomes observed in few small-scale human studies[5,6] led to wide-scale use of HY/AZ combination early in the pandemic. Several subsequent studies, however, did not corroborate the clinical efficacy of these drugs[8-11]; on the contrary, possible adverse cardiovascular effects were reported, casting serious doubts on the rationale for using these drugs in COVID-19 patients.[12-14]

Since both HY and AZ are known to prolong the QT-interval, their use alone or in combination has been the subject of intense debate.[15-17] Such concerns are even more valid in critically ill COVID-19 patients who often have concomitant myocardial injury.[18,19] There are conflicting reports on the magnitude of QTc prolongation with these drugs and its impact on adverse cardiac outcomes such as sudden cardiac death and torsade de pointes (TdP) in COVID-19 patients.[20-27] Small sample size and differences in infection severity are amongst the plausible explanations for the observed discrepancy between published reports. Whilst the use of HY to treat COVID-19 has largely been abandoned, safety concerns regarding its effect on QTc may potentially affect its use even within traditional indications such as SLE and malaria. This highlights the need for a large clinical study to clarify the effect of these medications on QT interval. [18,19,22,28] This retrospective, multi-centre study in a large cohort

of COVID-19 patients investigates the effect of HY therapy on QTc prolongation and any related ventricular arrhythmias or sudden arrhythmic deaths.

2 Methods

2.1 Patients

We identified all patients with confirmed SARS-CoV-2 infection consecutively admitted to eight hospitals of Abu Dhabi Health Services Company (SEHA) between March 1, 2020, and June 1, 2020, who received HY monotherapy or HY/AZ combination therapy as part of their treatment. COVID-19 testing was performed using reverse transcription-polymerase chain reaction (RT-PCR) assay. A detailed, retrospective chart review was performed by a team of cardiologists to assess baseline characteristics, pneumonia clinical severity and adverse events. Only patients with a baseline, pre-medication ECG as well as post-medication ECGs recorded no earlier than 24 hours after commencing treatment were included in the analysis. Patients receiving HY for less than 24 hrs or having follow-up ECG recorded within the first 24 hours of therapy or after discontinuation of therapy were excluded from analysis. This study was approved by the National Emirates Institutional Review Board for COVID research (DOH/CVDC/2020/831) and was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The requirement for informed consent was waived for this retrospective analysis. Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

2.2 Therapy regime

HY and AZ were given routinely to patients admitted with COVID-19 infection in the early days of the pandemic as part of the local COVID-19 treatment protocol. HY was administered orally at a dose of 400 mg twice for the first day (loading dose) followed by 200 mg twice a day. Patients on HY/AZ therapy also received AZ at a daily dose of 500 mg. As

per institution protocol, the duration of therapy was 5-7 days, but the final decision was left to the discretion of the treating physician.

2.3 QT measurements

ECG measurements were performed on a computer screen with digital callipers. Uncorrected QT and RR intervals were measured independently by two senior electrophysiologists and any discrepancy was resolved by agreement with a third electrophysiologist. The QT-interval was calculated using the tangent method[29] and the longest QT interval of all leads was recorded according to the guidelines.[30] The QT interval was reported daily (where available) for the first 5 days of treatment. The QT interval reported on day 5 was for the maximum QT interval on any ECG performed after day 4 while the patient was still on HY treatment. In patients with wide QRS (>120 ms) due to bundle branch block or paced rhythm, the QT-interval was corrected using the formula QT-(QRS-120).[31] QT intervals were rate corrected with the Bazett formula ($QTc_{(Bazett)}$). We also reported QTc using the Fridericia formula ($QTc_{(Fridericia)}$), since the Bazett formula is prone to overcorrection at higher heart rates.[32]

2.4 Outcomes

The primary outcome of interest was maximal QTc interval prolongation while on treatment. Severe QTc prolongation was defined as QTc ≥500 ms or an increase of ≥60 ms in QTc from the baseline value.[33] The main secondary outcomes were TdP/polymorphic ventricular tachycardia (VT), and sudden arrhythmic deaths.

2.5 Statistical Analysis

Baseline characteristics were summarized using descriptive statistics, including the mean and standard deviation for continuous measures and frequency tables for categorical variables. Categorical variables were compared using the chi-square or Fisher's exact test and continuous variables using the unpaired t-test or its non-parametric version (Wilcoxon rank-

sum test), if the assumption of normality was not met. The paired t-test was used for the main analysis when comparing QTc intervals between baseline and different time points. All statistical tests were two-sided, and p-values <0.05 were considered statistically significant. The statistical analysis was conducted using R software, version 3.6.1 (R Core Team, 2013).

3 Results

During the study period, a total of 12,276 COVID-19 patients were admitted to our medical centres and 7,502 of them received at least one dose of HY. Of these, 5,136 patients had an ECG performed only after HY therapy or had continuous QTc monitoring. There were 2,366 patients with at least two ECGs performed during the admission. We excluded a further 352 patients for not meeting other inclusion criteria, as defined in section 2.1. The final analysis involved 2,014 patients, of whom 1890 (94%) received HY monotherapy, and 124 (6%) received HY/AZ combination therapy (Figure 1).

The average age of patients was 46.8±12.6 years, and the majority of patients were male (85.8%). The average length of hospital stay (LOS) was 9.4±8.6 days (6 patients were still in hospital at the time of analysis), and the mean duration of HY treatment was 6.4±2.4 days. The LOS and duration of HY treatment were longer in the HY/AZ group than in the HY group. Overall, 36.5 % of the patients were diabetic, with no specific preponderance to any group. Patients with hypertension were more likely to be found in the HY group; there was no difference in the prevalence of chronic kidney disease, cancer, lung disease, structural heart disease, dialysis, or liver diseases in study groups. In total, 49 (2.4%) patients were immunocompromised, and the prevalence of such patients was higher in the HY/AZ group. Of all patients, 50 (2.5%) were asymptomatic, and 772 (38.3%), 736 (36.5%), and 456 (22.6%) had mild, moderate, and severe clinical severity, respectively. The HY/AZ group had more severely infected patients compared to HY (41.9% vs 21.4%). Patients requiring

admission to ICU, mechanical ventilation, inotropic support, or dialysis were also more prevalent in the HY/AZ group (Table 1).

The overall in-hospital mortality was 3.97% (80 patients), which was relatively higher in the HY/AZ group (5.65%) than in the HY group (3.86%); however, the difference did not reach statistical significance (p=0.46). Only 8 patients (10%) were receiving HY at the time of death. Sudden death was observed in only 4 patients (5%), all of whom were still receiving HY at the time of death. The cardiac arrest was due to asystole in 2 (2.5%) and pulseless electrical activity (PEA) in the other 2 patients (2.5%). In all remaining cases, a clear clinical deterioration in the hours preceding cardiorespiratory arrest was observed. Cardiac arrest was commonly caused by bradycardia and asystole (55/80 patients, 68.7%). PEA was the cause of cardiac arrest in 23 patients (28.8%), whereas monomorphic VT was observed only in 2 patients (2.5%), neither of whom was on HY at the time of death. There were no cases of polymorphic VT or TdP.

A modest but statistically significant QTc prolongation was observed during treatment. The mean $QTc_{(Bazett)}$ increased by 11.6 ms from 427.6±25.4 ms at baseline to 439.2±30.4 ms during therapy (p<0.001). $QTc_{(Fridericia)}$ had lower absolute numerical values compared to $QTc_{(Bazett)}$; however, the pattern of QTc increase was similar (baseline: 402.8±23.2, HY: 419.5±28.2 ms, p<0.001). The higher values with $QTc_{(Bazett)}$ were largely due to overcorrection during tachycardia since 441 (21.9%) patients had heart rate ≥100 BPM at baseline. Almost one-third of the patients had a decrease in QTc whilst on treatment, primarily due to the resolution of tachycardia with supportive treatment; hence this effect was more apparent with $QTc_{(Bazett)}$. QTc ≥500 ms and ΔQTc≥60 ms were observed in 3.3% and 4.5% of the patients, respectively, using Bazett formula, and in 1.7% and 5.5% of the patients, respectively, using Fridericia formula (Figure 2).

The temporal changes in QTc interval during HY therapy revealed a daily increase in both $QTc_{(Bazett)}$ and $QTc_{(Fridericia)}$ till day 3, after which the relative increase in QTc was less prominent (Figure 3). If maximal average $QTc_{(Bazett)}$ during the therapy is considered, there was an increase of 20.2 ms in the HY/AZ group and 11.0 ms in the HY group from their respective baseline values (p<0.001). A similar trend was observed in $QTc_{(Fridericia),}$ with an increase of 28.8 ms and 16.0 ms in the HY/AZ and HY groups, respectively (Figure 4).

Patients with more severe COVID-19 infection had greater QTc prolongation while on HY treatment. The observed $QTc_{(Bazett)}$ was significantly lower in survivors than it was in the deceased (438.4±29.9 ms vs. 459.8±21.4 ms, p<0.001). A similar trend was also observed using $QTc_{(Fridericia)}$. There was a systematic increase in $QTc_{(Bazett)}$ and $QTc_{(Fridericia)}$ values with increasing clinical infection severity. The mean values of $QTc_{(Bazett)}$ in asymptomatic, mild, moderate, and severely infected patients were 428.4±25.4, 432.3±27.2, 438.9±27.5, and 452.7±35.7 ms respectively (p<0.001); $QTc_{(Fridericia)}$ also exhibited a similar pattern (Figure 5).

4 Discussion

This large cohort study with paired ECG data suggests a clinically modest but statistically significant QTc prolongation after HY or HY/AZ therapy. Like other studies,[21,34] QTc prolongation was evident from the first day of therapy and showed an increasing daily trend suggestive of a possible cumulative effect. Notably, however, QTc prolongation was less marked than most other studies on COVID-19 patients[17,19] and was more in line with previous large-scale studies in patients with rheumatologic diseases.[26,35] Studies on COVID-19 patients reported a highly variable degree of QTc prolongation, which is unsurprising given the differences in sample size, demographics, and clinical severity in these studies.

These shortcomings were largely overcome in our study by virtue of its large sample size and covering different clinical severities.

In our cohort, the peak average QTc was higher in HY/AZ combination therapy than in HY monotherapy. This was expected since both drugs are known to prolong QTc interval.[36] In the combination therapy group, $QTc_{(Bazett)}$ increased from 431±25 ms to 451± 36 ms, whereas in the HY monotherapy group, the value increased only to 438±30 ms from a baseline value of 427± 25 ms. The QTc prolongation in the combination group is broadly similar to the 20-30 ms increase reported by several other investigators.[17,19,24,34] In our study, patients receiving combination therapy were more likely to have higher clinical COVID-19 severity and longer hospital stay. The need for ICU admission, mechanical ventilation, and inotropic support was also more likely in this group, reflecting a more turbulent clinical course. The frequent use of combination therapy in higher severity cases likely reflects the need for a more aggressive therapeutic approach in these patients.

The incidence of critical QTc prolongation was relatively low in our cohort. QTc>500 ms was observed in only 3.3% and 1.7% of the patients (Bazett and Fridericia, respectively). Approximately 5% of our patients manifested a ΔQTc≥60 ms, which is again on the lower side compared to other studies.[19] Hooks et al. reported a similar low incidence of 1.5% in rheumatologic patients on HY therapy.[26] In contrast, the incidence of severe QTc prolongation in literature from the COVID-19 era ranged between 11-36%, with most patients being treated with HY/AZ combination.[17,21,24,36] Such a variance can be attributed to the differences in the clinical severity and the demographics of the patients included in these studies and our younger cohort.[17,21]

Overall mortality in our study was 3.97%, with no significant difference between HY and the HY/AZ groups. No cases of polymorphic VT or TdP were observed while on treatment, and

sudden death occurred in only 4 cases (none were due to ventricular arrhythmia). The mortality rate in our study was significantly lower than the 21-27% mortality rate reported in other studies.[11,24,37] There are several possible explanations for this observation. In contrast with other studies, our study population was significantly younger, and HY was administered liberally irrespective of the clinical severity (i.e. use not restricted to severe cases). Another favourable factor in our case was that the healthcare system, coped well with the pandemic and was never overwhelmed; therefore, optimal care continued to be provided to all admitted patients. Finally, differences in the virulence of the virus strain may have been a contributing factor in explaining the differences in fatality rates observed in different parts of the world, though more research is needed to establish such a factor.

Our study highlights the effects of COVID-19 infection severity on QTc duration. Overall, QTc prolongation during treatment was more pronounced in patients with higher clinical severity. A stepwise increase in QTc interval during HY treatment was proportional to the increase in clinical severity from asymptotic to severe. Indeed, patients with the highest severity leading to fatality had the most prolonged QTc in the whole study (459.8±36.0 ms (Bazett), 432.8±34.2 ms (Fridericia)). Electrolyte abnormalities, myocardial injury, renal impairment, and polypharmacy are all more common in patients with severe infection, possibly compounding QTc prolongation.[38,39] Our observations highlight the multifactorial nature of QTc prolongation. The simultaneous presence of several QT-prolonging factors (such as drugs, genetic predisposition, electrolyte imbalance, severe illness) often has a synergistic effect, occasionally leading to marked QTc prolongation.[40]

To account for the impact of tachycardia frequently observed in COVID-19 patients on QTc calculations, we reported QTc measurements using both Bazett and Fridericia formulas. Indeed, in our study, almost a quarter of the patients were admitted with sinus tachycardia. The Fridericia formula probably offers better rate correction in this setting, a finding also

observed by Vandenberk et al.[32] Our results suggest that although there was a noticeable difference in the calculated QTc values by these two approaches, both showed a similar trend.

The demographics and patient characteristics in our study reflect the social structure and work-force distribution in UAE. The majority of patients in this study were Asian males, relatively young, but with a high prevalence of diabetes and hypertension. Many of these expatriate workers live in shared accommodation, possibly explaining the higher representation of Asian men among SARS-CoV-2 infected patients in our study.

Finally, our results may not be relevant anymore to the treatment of COVID-19 patients given the rapid decline in the use of HY and AZ in this group. However, the fact that our population was younger and with a lower clinical severity compared to other studies may make our results more relevant during HY treatment for other conditions such as malaria and SLE.

4.1 Strength and Limitations

To date, this is the largest, multi-centre study with paired ECG data examining the effects of HY on QTc prolongation. Another strength of the study is the inclusion of patients with different clinical severity levels. Therefore, the effects of HY on QTc in our study are more applicable to a wider population compared to previous studies predominantly recruiting Caucasian patients with severe infection. Our study also reports QTc values by two methods and, therefore, factors in the effect of heart rate on QTc measurements.

One of the major limitations of the study is its retrospective design and the absence of a control group. ECG data collection from a drug-free control group was not possible due to the liberal use of HY in our hospitals as well as the need to limit unnecessary ECG requests to protect staff. However, the lack of a control group was compensated for by the paired nature of our measurements reducing the inter-subject variability. In addition, we do not have an AZ

only group; hence, we cannot comment on its isolated effect on QTc. Furthermore, there may be a degree of selection bias with ECGs potentially being recorded in patients deemed to be at higher risk of QT prolongation. In addition, due to the large sample size and retrospective nature of the study, it was not possible to confirm whether patients were receiving other QT-prolonging drugs during HY therapy. However, the institutional protocol for HY therapy mandated regular monitoring of drug interactions by clinical pharmacists thereby limiting the impact of this factor. Finally, data is mainly from patients with COVID-19 infection with a strong male preponderance, possibly limiting the generalizability of the study findings to females and non-COVID-19 patients.

5 Conclusion

Among COVID-19 patients prescribed HY alone or in combination with AZ, there was a modest QTc prolongation. The incidence of extreme QTc prolongation was low and not associated with any major drug-induced cardiovascular events. Although the use of HY to treat COVID-19 has largely been abandoned, it remains widely indicated to treat other conditions. Thus, when HY is used appropriately and with adequate cardiac monitoring, it remains a safe drug with only a trivial risk of significant adverse cardiac events. Caution should, however, be exercised with the concomitant use of HY with other QT-prolonging drugs or very sick patients.

Contributorship Statement

MEK contributed to the study design, literature search, data collection, drafting the manuscript, data analysis and interpretation. OF and SAK contributed to the study design, critical review of the manuscript, data collection and interpretation. RA contributed to data collection and interpretation, drafting and critical review of the manuscript. AO contributed to statistical analysis, drafting the figures and critical review of the manuscript. All other authors contributed to data collection and editing and review of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. MEK accepts responsibility as guarantor.

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Conflict of Interest

MEK has received honoraria for consultancy for Medtronic, Abbott, Pfizer, Bayer, Saja, and Boehringer Ingelheim. SAK has received honoraria for consultancy for Medtronic, Bayer, Pfizer and Saja. OF has received honoraria for consultancy for Medtronic. None of the above interests are related to this article. All other authors declare no competing interests.

Data sharing

Individual participant data will be made available on request, directed to the corresponding author (MEK). Requests will be assessed for scientific rigour before being granted. After

approval of a proposal, data will be anonymised and securely transferred. A data sharing agreement may be required.

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Figure legends

Figure 1: Flowchart of study participants included in the analysis

Figure 2: Changes in QTc interval in patients treated with HY (with or without AZ). Panels (a) and (b) show baseline and peak QTc interval using Bazett and Fridericia formulas, respectively. Panels (c) and (d) show distribution of patients stratified by degree of QTc change using Bazett and Fridericia formulas, respectively.

Figure 3: Baseline and daily QTc interval change in patients treated with HY (with or without AZ) using (a) Bazett and (b) Fridericia formulas, respectively.

Figure 4: Baseline and maximal QTc measurements in patients treated with HY alone or in association with AZ using (a) Bazett and (b) Fridericia formulas, respectively.

Figure 5: Relationship between QTc and mortality and disease severity. Panels (a) and (b) display maximal QTc interval in survivors and deceased patients (Bazett and Fridericia formulas, respectively). Distribution of maximal QTc intervals stratified by clinical severity of COVID-19 infection is shown in panels (c) and (d) using Bazett and Fridericia formulas, respectively.

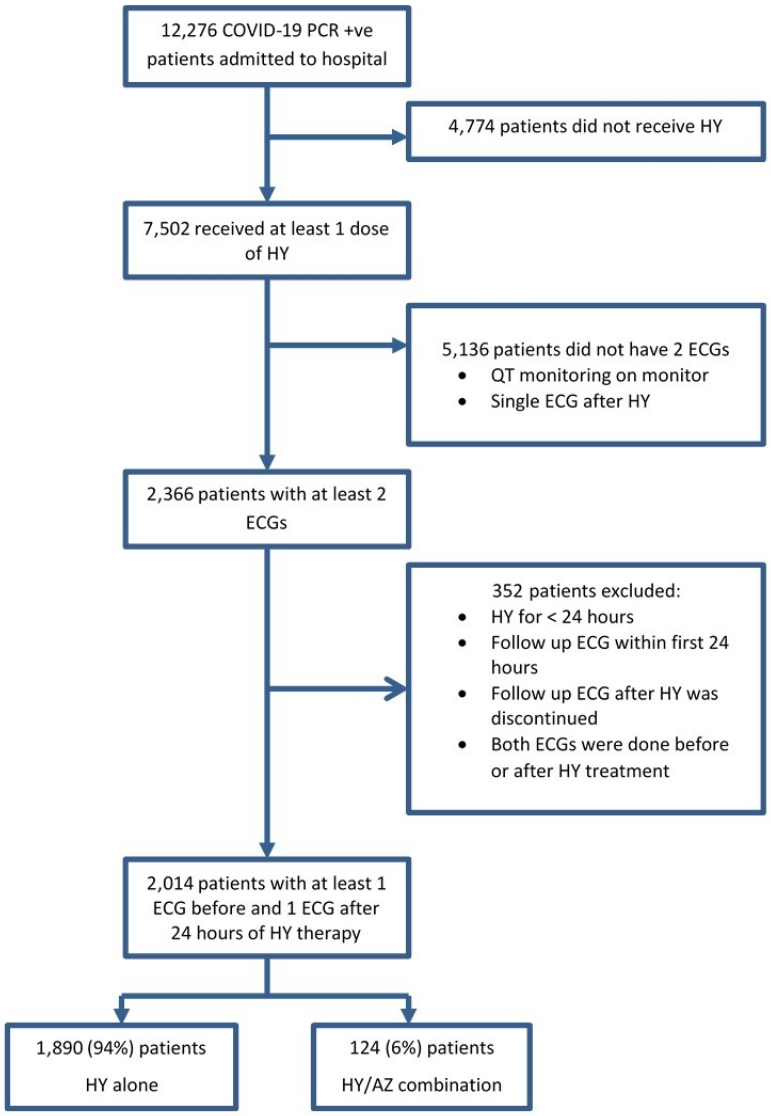
Table 1: Baseline characteristics, risk factors and clinical course of patients

Baseline Characteristics and Clinical Course				
	Total 2,014 (100%)	HY only 1,890 (94%)	HY/AZ 124 (6%)	P value †
Baseline Characteristics				
Age, Mean (±SD)	46.8 (±12.6)	47.0 (±12.6)	43.8 (±12.2)	0.005
Male Sex, n (%)	1,727 (85.7%)	1,619 (85.6%)	108 (87.1%)	0.756
Ethnicity, n (%)				
• African	15 (0.7%)	15 (0.8%)	0 (0.0%)	0.686
• Arab	367 (18.2%)	342 (18.1%)	25 (20.3%)	
• Asian	1,612 (80.2%)	1,515 (80.3%)	97 (78.3%)	
• Caucasian	11 (0.5%)	10 (0.5%)	1 (0.8%)	
• Other	7 (0.4%)	6 (0.3%)	1 (0.8%)	
Length of Stay (days), Mean (±SD)	9.4 (±8.6)	9.0 (±8.3)	15.2 (±10.7)	<0.001
Length of HY treatment (Days), Mean (±SD)	6.4 (±2.3)	6.3 (±2.3)	7.6 (±2.7)	<0.001
Clinical Risk Factors				
BMI, Mean (±SD)	27.6 (±5.0)	27.7 (±5.1)	26.4 (±4.6)	0.003
BMI Categories, n (%)				
• < 25	593 (33.3%)	549 (32.9%)	44 (39.3%)	0.057
• 25-30	711 (39.9%)	662 (39.7%)	49 (43.7%)	
• 30-40	425 (23.9%)	406 (24.3%)	19 (17.0%)	
• > 40	51 (2.9%)	51 (3.1%)	0 (0.0%)	

Smoking Status, n (%)				
• Current smoker	109 (5.4%)	107 (5.7%)	2 (1.6%)	0.028
• Former smoker	74 (3.7%)	73 (3.9%)	1 (0.8%)	
• Non smoker	1,831 (90.9%)	1,710 (90.4%)	121 (97.6%)	
Diabetes, n (%)	736 (36.5%)	695 (36.8%)	41 (33.1%)	0.463
Hypertension, n (%)	786 (39.0%)	749 (39.6%)	37 (29.8%)	0.038
CKD, n (%)	141 (7.0%)	132 (6.9%)	9 (7.3%)	1.000
Cancer, n (%)	49 (2.5%)	45 (2.4%)	4 (3.2%)	0.771
Lung disease, n (%)	118 (5.9%)	113 (6.0%)	5 (4.0%)	0.486
Structural heart disease, n (%)	155 (7.7%)	150 (7.9%)	5 (4.0%)	0.160
Liver disease, n (%)	15 (0.7%)	14 (0.7%)	1 (0.8%)	1.000
Immunosuppression, n (%)	49 (2.4%)	42 (2.2%)	7 (5.6%)	0.036
Clinical Course				
Clinical severity, n (%)				
• Asymptomatic	50 (2.5%)	46 (2.4%)	4 (3.2%)	<0.001
• Mild	772 (38.3%)	731 (38.7%)	41 (33.1%)	
• Moderate	736 (36.6%)	709 (37.5%)	27 (21.8%)	
• Severe	456 (22.6%)	404 (21.4%)	52 (41.9%)	
CXR findings, n (%)				
• Consolidation	1,390 (69.0%)	1,294 (68.5%)	96 (77.4%)	0.031
• No consolidation	251 (12.5%)	235 (12.4%)	16 (12.9%)	
• CXR not performed	373 (18.5%)	361 (19.1%)	12 (9.7%)	
Lung CT findings, n (%)				
• Normal	80 (4.0%)	73 (3.7%)	7 (5.6%)	<0.001

• Mild changes	523 (26.0%)	496 (26.3%)	27 (21.8%)	
• Moderate changes	785 (39.0%)	758 (40.2%)	27 (21.8%)	
• Severe changes	209 (10.3%)	192 (10.2%)	17 (13.7%)	
• Lung CT not performed	417 (20.7%)	371 (19.6%)	46 (37.1%)	
ICU admission, n (%)	241 (11.2%)	209 (11.1%)	32 (25.8%)	<0.001
Mechanical ventilation, n (%)	190 (9.4%)	166 (8.8%)	24 (19.3%)	<0.001
Inotropes, n (%)	183 (9.0%)	160 (8.4%)	23 (18.5%)	<0.001
Dialysis, n (%)	90 (4.5%)	82 (4.3%)	8 (6.4%)	0.379
Mortality, n (%)	80 (3.97%)	73 (3.86%)	7 (5.65%)	0.455

† Continuous variables were summarized using the t-test, while discrete variables were summarized using the Chi-square test.



Flowchart of study participants included in the analysis

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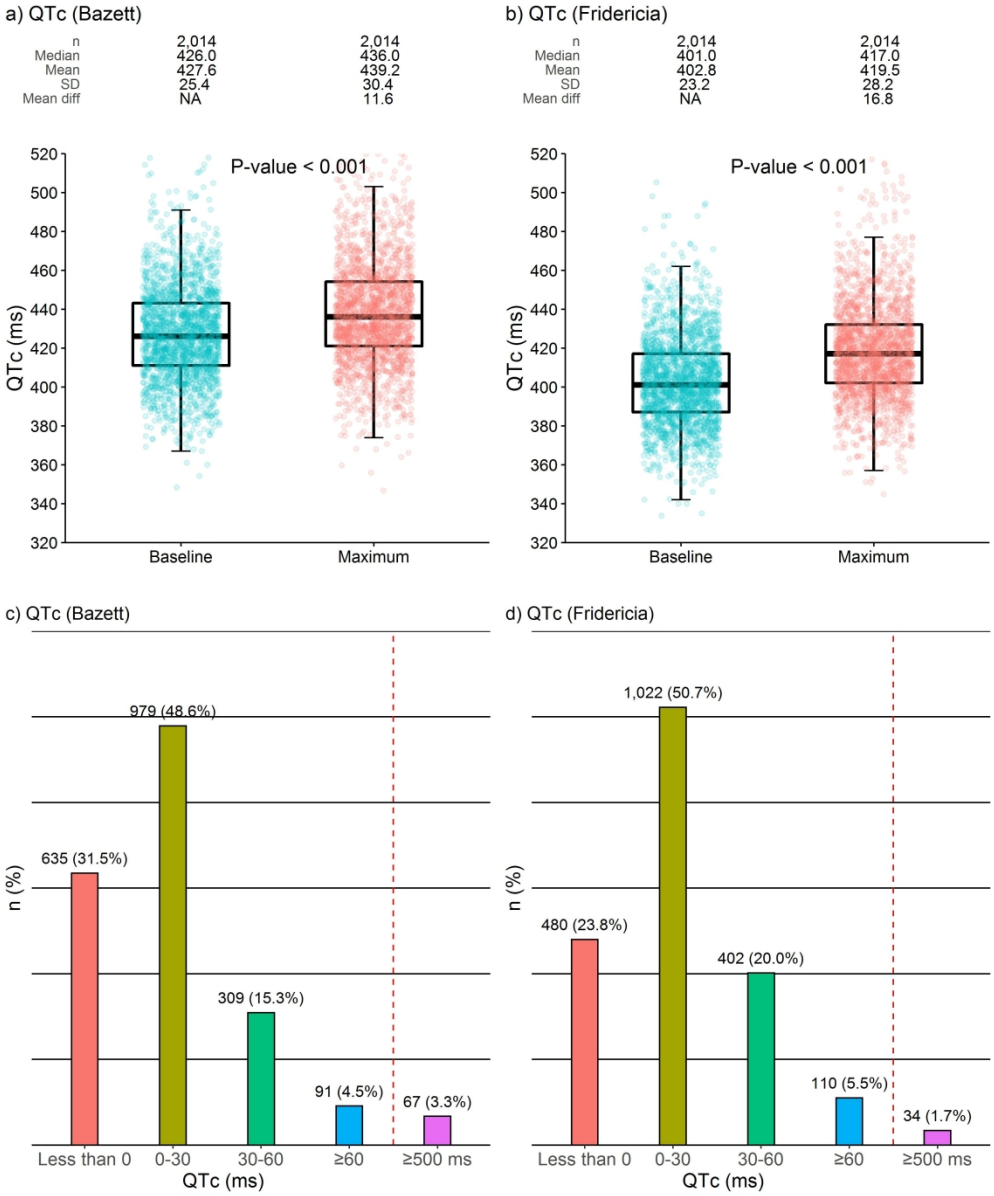
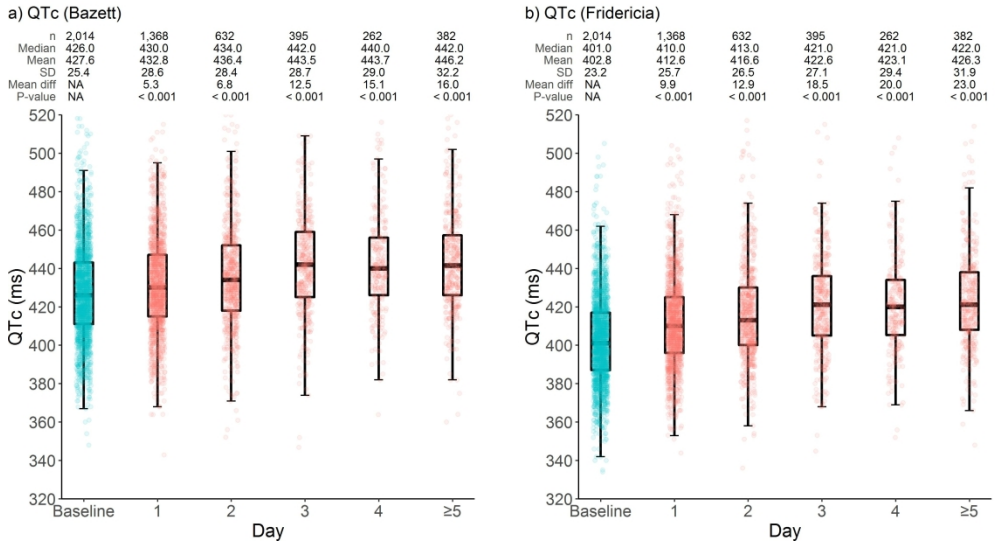


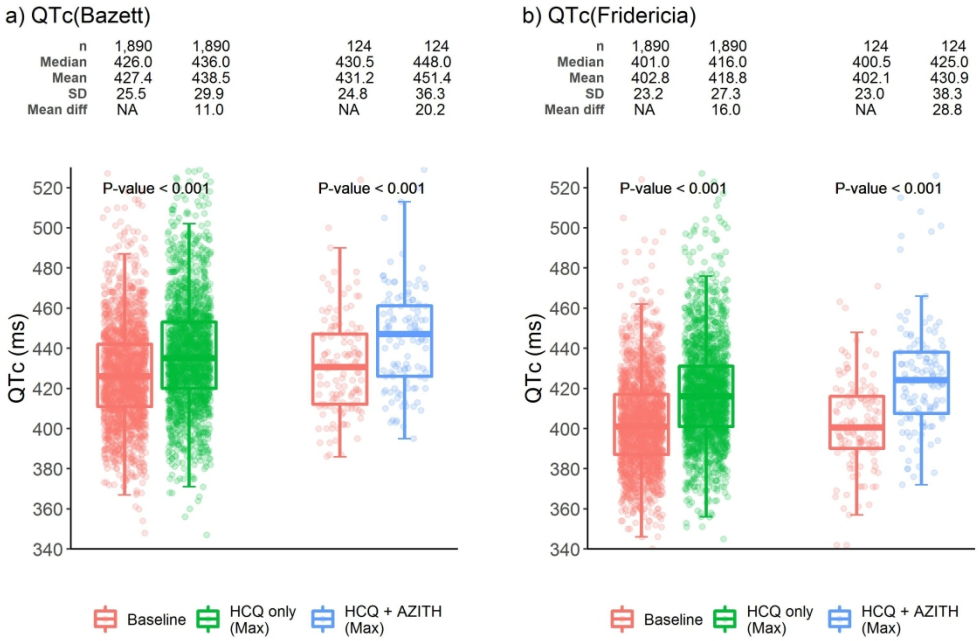
Changes in QTc interval in patients treated with HY (with or without AZ). Panels (a) and (b) show baseline and peak QTc interval using Bazett and Fridericia formulas, respectively. Panels (c) and (d) show distribution of patients stratified by degree of QTc change using Bazett and Fridericia formulas, respectively.

254x304mm (350 x 350 DPI)



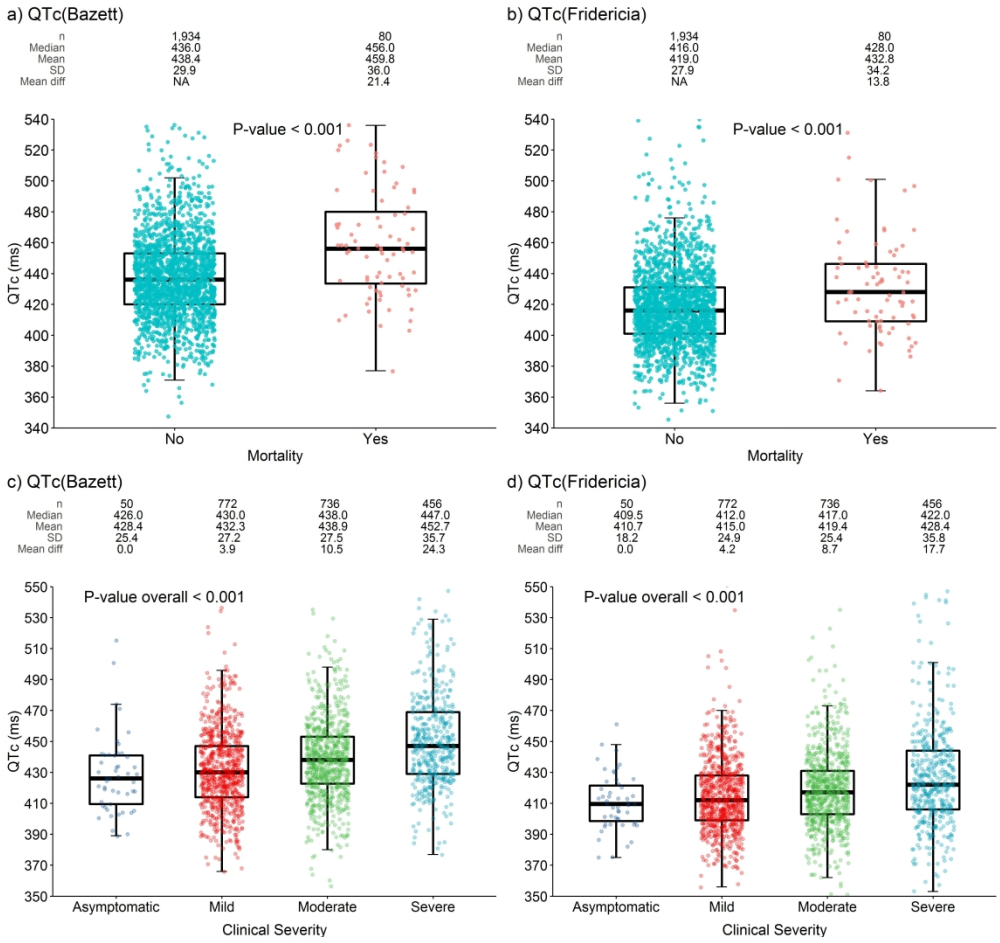
Baseline and daily QTc interval change in patients treated with HY (with or without AZ) using (a) Bazett and (b) Fridericia formulas, respectively.

304x165mm (350 x 350 DPI)



Baseline and maximal QTc measurements in patients treated with HY alone or in association with AZ using (a) Bazett and (b) Fridericia formulas, respectively.

228x152mm (350 x 350 DPI)



Relationship between QTc and mortality and disease severity. Panels (a) and (b) display maximal QTc interval in survivors and deceased patients (Bazett and Fridericia formulas, respectively). Distribution of maximal QTc intervals stratified by clinical severity of COVID-19 infection is shown in panels (c) and (d) using Bazett and Fridericia formulas, respectively.

381x355mm (350 x 350 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6*
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	6-7
		(*d*) If applicable, explain how loss to follow-up was addressed	6-7
		(*e*) Describe any sensitivity analyses	NA
Results			NA

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	8-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Changes in QTc Interval After Hydroxychloroquine Therapy in Patients with COVID-19 Infection: a Large, Retrospective, Multi-centre Cohort study

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Keywords:	COVID-19, Adult cardiology < CARDIOLOGY, CLINICAL PHARMACOLOGY

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Changes in QTc Interval After Hydroxychloroquine Therapy in Patients with COVID-19 Infection: a Large, Retrospective, Multi-centre Cohort study

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ABSTRACT

Objective: To evaluate the extent of hydroxychloroquine induced QTc prolongation and its relation to COVID-19 infection severity, the incidence of polymorphic ventricular arrhythmias and sudden arrhythmic deaths.

Design: A large-scale cohort study with retrospective analysis of baseline and on-therapy QT interval corrected using Bazett and Fridericia formulas.

Setting: A multicentre study involving eight secondary and tertiary care hospitals of the Abu Dhabi Health Services Company (SEHA), UAE

Participants: 2,014 patients consecutively admitted with PCR confirmed SARS-CoV-2 infection between March 1, 2020, and June 1, 2020

Interventions: Treatment with hydroxychloroquine alone or in combination with azithromycin for at least 24 hours and with a baseline ECG and at least 1 ECG after 24 hours of therapy.

Main outcome measures: Maximal QTc interval prolongation and its relationship to clinical severity, polymorphic ventricular tachycardia (VT) and sudden arrhythmic deaths while on treatment.

Results: the baseline $QTc_{(Bazett)}$ was 427.6±25.4 ms, and the maximum $QTc_{(Bazett)}$ during treatment was 439.2±30.4 ms (p<0.001). Severe QTc prolongation (QTc ≥500 ms) was observed in 1.7-3.3% of patients (Fridericia and Bazett, respectively), There were no cases of polymorphic ventricular arrhythmia or hydroxychloroquine related arrhythmic deaths. QTc prolongation was more pronounced in combination therapy compared to hydroxychloroquine alone (22.2 ms vs. 11.0 ms, p<0.001) and in patients with higher COVID-19 clinical severity (asymptomatic: 428.4±25.4 ms, severe COVID-19 infection: 452.7±35.7 ms, p<0.001). The

overall in-hospital mortality was 3.97%, and deceased patients had longer on-therapy $QTc_{(Bazett)}$ than survivors (459.8±21.4 ms vs. 438.4±29.9 ms, $p<0.001$).

Conclusions: The incidence of severe QTc prolongation with HY was low and not associated with ventricular arrhythmia. The safety concerns surrounding the use of HY may have been overestimated; however, caution should be exercised when using HY in patients with risk factors for QT prolongation.

Keywords: COVID-19, QT-interval, QTc, hydroxychloroquine, azithromycin

Strengths and limitations of the study:

- To date, this is the largest, multi-centre study with paired ECG data examining the effects of HY on QTc prolongation.
- The study explores the link between clinical disease severity and QTc interval prolongation
- The study population included patients with different clinical severity levels; hence, the effects of HY on QTc in our study are more applicable to a wider population.
- The retrospective design of the study, the absence of a control group and the strong male preponderance are limitations to this study which was performed during the first wave of the COVID-19 pandemic.

1 Introduction

The coronavirus disease 2019 (COVID-19) pandemic brought unprecedented diagnostic and therapeutic challenges to the world. Until a proven disease-specific treatment is available, repurposing of available drugs is amongst the few options available to reduce its mortality and morbidity.[1]

Hydroxychloroquine (HY) is a commonly used antimalarial agent frequently prescribed for rheumatoid arthritis and systemic lupus erythematosus (SLE). Azithromycin (AZ) is a macrolide antibiotic with well-described anti-inflammatory and immunomodulatory properties.[2] The antiviral efficacy of HY against SARS-CoV 2 in some in-vitro studies[3,4] along with favourable outcomes observed in few small-scale human studies[5,6] led to wide-scale use of HY/AZ combination early in the pandemic[7]. Several subsequent studies, however, did not corroborate the clinical efficacy of these drugs[8-11]; on the contrary, possible adverse cardiovascular effects were reported, casting serious doubts on the rationale for using these drugs in COVID-19 patients.[12-14]

Since both HY and AZ are known to prolong the QT-interval, their use alone or in combination has been the subject of intense debate.[15-17] Such concerns are even more valid in critically ill COVID-19 patients who often have concomitant myocardial injury.[18,19] While most studies reported QTc prolongation with these drugs, the magnitude of this prolongation and its impact on adverse cardiac outcomes such as sudden cardiac death and torsade de pointes (TdP) was variable between different studies.[20-27] For example, The incidence of extreme QTc prolongation (a marker of sudden cardiac death) varied between 2.7% and 36% depending on the study. [17,25] Small sample size and differences in infection severity are amongst the plausible explanations for the observed discrepancy between published reports. Whilst the use of HY to treat COVID-19 has largely been abandoned, safety concerns regarding its effect on QTc may potentially affect its use even within traditional indications

such as SLE and malaria. This highlights the need for a large clinical study to clarify the effect of these medications on QT interval. [18,19,22,28] This retrospective, multi-centre study in a large cohort of COVID-19 patients investigates the effect of HY therapy on QTc prolongation and any related ventricular arrhythmias or sudden arrhythmic deaths.

2 Methods

2.1 Patients

We identified all patients with confirmed SARS-CoV-2 infection consecutively admitted to eight hospitals of Abu Dhabi Health Services Company (SEHA) between March 1, 2020, and June 1, 2020, who received HY monotherapy or HY/AZ combination therapy as part of their treatment. COVID-19 testing was performed using reverse transcription-polymerase chain reaction (RT-PCR) assay. A detailed, retrospective chart review was performed by a team of cardiologists to assess baseline characteristics, pneumonia clinical severity and adverse events. Only patients with a baseline, pre-medication ECG as well as post-medication ECGs recorded no earlier than 24 hours after commencing treatment were included in the analysis. Patients receiving HY for less than 24 hrs or having follow-up ECG recorded within the first 24 hours of therapy or after discontinuation of therapy were excluded from analysis.

2.2 Therapy regime

HY and AZ were given routinely to patients admitted with COVID-19 infection in the early days of the pandemic as part of the local COVID-19 treatment protocol. HY was administered orally at a dose of 400 mg twice for the first day (loading dose) followed by 200 mg twice a day. Patients on HY/AZ therapy also received AZ at a daily dose of 500 mg. As per institution protocol, the duration of therapy was 5-7 days, but the final decision was left to the discretion of the treating physician.

2.3 QT measurements

ECG measurements were performed on a computer screen with digital callipers. Uncorrected QT and RR intervals were measured independently by two senior electrophysiologists and any discrepancy was resolved by agreement with a third electrophysiologist. The QT-interval was calculated using the tangent method[29] and the longest QT interval of all leads was recorded according to the guidelines.[30] The QT interval was reported daily (where available) for the first 5 days of treatment. The QT interval reported on day 5 was for the maximum QT interval on any ECG performed after day 4 while the patient was still on HY treatment. In patients with wide QRS (>120 ms) due to bundle branch block or paced rhythm, the QT-interval was corrected using the formula QT-(QRS-120).[31] QT intervals were rate corrected with the Bazett formula ($QTc_{(Bazett)}$). We also reported QTc using the Fridericia formula ($QTc_{(Fridericia)}$), since the Bazett formula is prone to overcorrection at higher heart rates.[32]

2.4 Outcomes

The primary outcome of interest was maximal QTc interval prolongation while on treatment. Severe QTc prolongation was defined as QTc ≥500 ms or an increase of ≥60 ms in QTc from the baseline value.[33] The main secondary outcomes were TdP/polymorphic ventricular tachycardia (VT), and sudden arrhythmic deaths.

2.5 Statistical Analysis

Baseline characteristics were summarized using descriptive statistics, including the mean and standard deviation for continuous measures and frequency tables for categorical variables. Categorical variables were compared using the chi-square or Fisher's exact test and continuous variables using the unpaired t-test or its non-parametric version (Wilcoxon rank-sum test), if the assumption of normality was not met. The paired t-test was used for the main analysis when comparing QTc intervals between baseline and different time points.

We also carried out a series of multiple linear regression models to investigate the association between mortality and severity of COVID-19 from one side and QTc prolongation from another side. In these models, the worst QTc was considered as the dependent variable and was regressed against each of the main independent variables (i.e. mortality and severity of COVID-19), adjusting for available potential confounders such as age, BMI, gender and comorbidity. All statistical tests were two-sided, and p-values <0.05 were considered statistically significant. The statistical analysis was conducted using R software, version 3.6.1 (R Core Team, 2013).

2.6 Patient and public involvement

Patients and the public were not involved in the design, conduct, or reporting of this research in view of its retrospective nature.

3 Results

During the study period, a total of 12,276 COVID-19 patients were admitted to our medical centres and 7,502 of them received at least one dose of HY. Of these, 5,136 patients had an ECG performed only after HY therapy or had continuous QTc monitoring. There were 2,366 patients with at least two ECGs performed during the admission. We excluded a further 352 patients for not meeting other inclusion criteria, as defined in section 2.1. The final analysis involved 2,014 patients, of whom 1890 (94%) received HY monotherapy, and 124 (6%) received HY/AZ combination therapy (Figure 1).

The average age of patients was 46.8±12.6 years, and the majority of patients were male (85.8%). The average length of hospital stay (LOS) was 9.4±8.6 days (6 patients were still in hospital at the time of analysis), and the mean duration of HY treatment was 6.4±2.4 days. The LOS and duration of HY treatment were longer in the HY/AZ group than in the HY

group. Overall, 36.5 % of the patients were diabetic, with no specific preponderance to any group. Patients with hypertension were more likely to be found in the HY group; there was no difference in the prevalence of chronic kidney disease, cancer, lung disease, structural heart disease, dialysis, or liver diseases in study groups. In total, 49 (2.4%) patients were immunocompromised, and the prevalence of such patients was higher in the HY/AZ group. Of all patients, 50 (2.5%) were asymptomatic, and 772 (38.3%), 736 (36.5%), and 456 (22.6%) had mild, moderate, and severe clinical severity, respectively. The HY/AZ group had more severely infected patients compared to HY (41.9% vs 21.4%). Patients requiring admission to ICU, mechanical ventilation, inotropic support, or dialysis were also more prevalent in the HY/AZ group (Table 1).

The overall in-hospital mortality was 3.97% (80 patients), which was relatively higher in the HY/AZ group (5.65%) than in the HY group (3.86%); however, the difference did not reach statistical significance (p=0.46). Only 8 patients (10%) were receiving HY at the time of death. Sudden death was observed in only 4 patients (5%), all of whom were still receiving HY at the time of death. The cardiac arrest was due to asystole in 2 (2.5%) and pulseless electrical activity (PEA) in the other 2 patients (2.5%). In all remaining cases, a clear clinical deterioration in the hours preceding cardiorespiratory arrest was observed. Cardiac arrest was commonly caused by bradycardia and asystole (55/80 patients, 68.7%). PEA was the cause of cardiac arrest in 23 patients (28.8%), whereas monomorphic VT was observed only in 2 patients (2.5%), neither of whom was on HY at the time of death. There were no cases of polymorphic VT or TdP.

A modest but statistically significant QTc prolongation was observed during treatment. The mean $QTc_{(Bazett)}$ increased by 11.6 ms from 427.6±25.4 ms at baseline to 439.2±30.4 ms during therapy (p<0.001). $QTc_{(Fridericia)}$ had lower absolute numerical values compared to

$QTc_{(Bazett)}$; however, the pattern of QTc increase was similar (baseline: 402.8±23.2, HY: 419.5±28.2 ms, $p<0.001$). The higher values with $QTc_{(Bazett)}$ were largely due to overcorrection during tachycardia since 441 (21.9%) patients had heart rate ≥100 BPM at baseline. Almost one-third of the patients had a decrease in QTc whilst on treatment, primarily due to the resolution of tachycardia with supportive treatment; hence this effect was more apparent with $QTc_{(Bazett)}$. QTc ≥500 ms and ΔQTc≥60 ms were observed in 3.3% and 4.5% of the patients, respectively, using Bazett formula, and in 1.7% and 5.5% of the patients, respectively, using Fridericia formula (Figure 2).

The temporal changes in QTc interval during HY therapy revealed a daily increase in both $QTc_{(Bazett)}$ and $QTc_{(Fridericia)}$ till day 3, after which the relative increase in QTc was less prominent (Figure 3). In the HY/AZ combination therapy group, $QTc_{(Bazett)}$ increased from 431±25 ms to 451± 36 ms, whereas in the HY monotherapy group, the value increased only to 438±30 ms from a baseline value of 427± 25 ms. A similar trend was observed in $QTc_{(Fridericia)}$, with an increase of 28.8 ms and 16.0 ms in the HY/AZ and HY groups, respectively (Figure 4).

Patients with more severe COVID-19 infection had greater QTc prolongation while on HY treatment. The observed $QTc_{(Bazett)}$ was significantly lower in survivors than it was in the deceased (438.4±29.9 ms vs. 459.8±21.4 ms, $p<0.001$). A similar trend was also observed using $QTc_{(Fridericia)}$. There was a systematic increase in $QTc_{(Bazett)}$ and $QTc_{(Fridericia)}$ values with increasing clinical infection severity. The mean values of $QTc_{(Bazett)}$ in asymptomatic, mild, moderate, and severely infected patients were 428.4±25.4, 432.3±27.2, 438.9±27.5, and 452.7±35.7 ms respectively ($p<0.001$); $QTc_{(Fridericia)}$ also exhibited a similar pattern (Figure 5). The associations between $QTc_{(Bazett)}$ and $QTc_{(Fridericia)}$ from one side and mortality and severity of COVID-19 from another side were still statistically significant when multiple

linear regression models adjusting for age, gender, BMI and comorbidity were used. The details of these adjusted analyses are reported in the supplementary material (Supplementary Tables 1, 2, 3 and 4).

4 Discussion

This large cohort study with paired ECG data suggests a clinically modest but statistically significant QTc prolongation after HY or HY/AZ therapy. Like other studies,[21,34] QTc prolongation was evident from the first day of therapy and showed an increasing daily trend suggestive of a possible cumulative effect. Notably, however, QTc prolongation was less marked than most other studies on COVID-19 patients[17,19] and was more in line with previous large-scale studies in patients with rheumatologic diseases.[26,35] Studies on COVID-19 patients reported a highly variable degree of QTc prolongation, which is unsurprising given the differences in sample size, demographics, and clinical severity in these studies. These shortcomings were largely overcome in our study by virtue of its large sample size and covering different clinical severities.

In our cohort, the peak average QTc was higher in HY/AZ combination therapy than in HY monotherapy. This was expected since both drugs are known to prolong QTc interval.[36] In the combination therapy group, there was a 20.2 ms increase in $QTc_{(Bazett)}$ in the HY/AZ group and 11.0 ms in the HY group from their respective baseline values ($p<0.001$). This QTc prolongation in the combination group is broadly similar to the 20-30 ms increase reported by several other investigators.[17,19,24,34] In our study, patients receiving combination therapy were more likely to have higher clinical COVID-19 severity and longer hospital stay. The need for ICU admission, mechanical ventilation, and inotropic support was also more likely in this group, reflecting a more turbulent clinical course. The frequent use of combination therapy in

higher severity cases likely reflects the need for a more aggressive therapeutic approach in these patients.

The incidence of critical QTc prolongation was relatively low in our cohort compared to other studies.[19] Hooks et al. reported a similar low incidence of 1.5% in rheumatologic patients on HY therapy.[26] In contrast, the incidence of severe QTc prolongation in literature from the COVID-19 era ranged between 11-36%, with most patients being treated with HY/AZ combination.[17,21,24,36] Such a variance can be attributed to the differences in the clinical severity and the demographics of the patients included in these studies and our younger cohort.[17,21]

Overall mortality in our study was 3.97%, with no cases of polymorphic VT, TdP or sudden death due to ventricular arrhythmia. The mortality rate in our study was significantly lower than the 21-27% mortality rate reported in other studies.[11,24,37] There are several possible explanations for this observation. In contrast with other studies, our study population was significantly younger, and HY was administered liberally irrespective of the clinical severity (i.e. use not restricted to severe cases). Another favourable factor in our case was that the healthcare system, coped well with the pandemic and was never overwhelmed; therefore, optimal care continued to be provided to all admitted patients. Finally, differences in the virulence of the virus strain may have been a contributing factor in explaining the differences in fatality rates observed in different parts of the world, though more research is needed to establish such a factor.

Our study highlights the effects of COVID-19 infection severity on QTc duration. Overall, QTc prolongation during treatment was more pronounced in patients with higher clinical severity. A stepwise increase in QTc interval during HY treatment was proportional to the increase in clinical severity from asymptotic to severe. Indeed, patients with the highest

severity leading to fatality had the most prolonged QTc in the whole study (459.8±36.0 ms (Bazett), 432.8±34.2 ms (Fridericia)). Electrolyte abnormalities, myocardial injury, renal impairment, and polypharmacy are all more common in patients with severe infection, possibly compounding QTc prolongation.[38,39] Our observations highlight the multifactorial nature of QTc prolongation. The simultaneous presence of several QT-prolonging factors (such as drugs, genetic predisposition, electrolyte imbalance, severe illness) often has a synergistic effect, occasionally leading to marked QTc prolongation.[40]

To account for the impact of tachycardia frequently observed in COVID-19 patients on QTc calculations, we reported QTc measurements using both Bazett and Fridericia formulas. Indeed, in our study, almost a quarter of the patients were admitted with sinus tachycardia. The Fridericia formula probably offers better rate correction in this setting, a finding also observed by Vandenberk et al.[32] Our results suggest that although there was a noticeable difference in the calculated QTc values by these two approaches, both showed a similar trend.

The demographics and patient characteristics in our study reflect the social structure and work-force distribution in UAE. The majority of patients in this study were Asian males, relatively young, but with a high prevalence of diabetes and hypertension. Many of these expatriate workers live in shared accommodation, possibly explaining the higher representation of Asian men among SARS-CoV-2 infected patients in our study.

The main strength of this study is that it is the largest, multi-centre study to date with paired ECG data examining the effects of HY on QTc prolongation. Another strength of the study is the inclusion of patients with different clinical severity levels. Therefore, the effects of HY on QTc in our study are more applicable to a wider population compared to previous studies predominantly recruiting Caucasian patients with severe infection. Our study also reports QTc values by two methods and, therefore, factors in the effect of heart rate on QTc

measurements. One of the major limitations of the study is its retrospective design and the absence of a control group. ECG data collection from a drug-free control group was not possible due to the liberal use of HY in most COVID-19 patients in our hospitals at that time. In addition, it was difficult to justify performing non-clinically indicated ECGs in a control group at a time when healthcare resources were already overstretched and it was vital to protect staff by reducing unnecessary exposure to COVID-19 patients. However, the lack of a control group was compensated for by the paired nature of our measurements reducing the inter-subject variability. In addition, since AZ was used only as an additional therapy to HY and not as monotherapy, we do not have an AZ only group; hence, we cannot comment on its isolated effect on QTc. Furthermore, there may be a degree of selection bias with ECGs potentially being recorded in patients deemed to be at higher risk of QT prolongation. In addition, due to the large sample size and retrospective nature of the study, it was not possible to confirm whether patients were receiving other QT-prolonging drugs during HY therapy. However, the institutional protocol for HY therapy mandated regular monitoring of drug interactions by clinical pharmacists thereby limiting the impact of this factor. Moreover, our data is mainly from patients with COVID-19 infection with a strong male preponderance, possibly limiting the generalizability of the study findings to females and non-COVID-19 patients. Finally, our results may not be relevant anymore to the treatment of COVID-19 patients given the rapid decline in the use of HY and AZ in this group. However, the fact that our population was younger and with a lower clinical severity compared to other studies may make our results more relevant during HY treatment for other conditions such as malaria and SLE.

5 Conclusion

Among COVID-19 patients prescribed HY alone or in combination with AZ, there was a modest QTc prolongation. The incidence of extreme QTc prolongation was low and not associated with any major drug-induced cardiovascular events. Although the use of HY to treat COVID-19 has largely been abandoned, it remains widely indicated to treat other conditions. Thus, when HY is used appropriately and with adequate cardiac monitoring, it remains a safe drug with only a trivial risk of significant adverse cardiac events. Caution should, however, be exercised with the concomitant use of HY with other QT-prolonging drugs or very sick patients.

Contributorship Statement

MEK contributed to the study design, literature search, data collection, drafting the manuscript, data analysis and interpretation. OF and SAK contributed to the study design, critical review of the manuscript, data collection and interpretation. RA contributed to data collection and interpretation, drafting and critical review of the manuscript. AO contributed to statistical analysis, drafting the figures and critical review of the manuscript. AAA, ZA, AH, BP, SA, HB, AA, MS and YA contributed to data collection and editing and review of the manuscript. The corresponding author (MEK) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. MEK accepts responsibility as guarantor.

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Conflict of Interest

MEK has received honoraria for consultancy for Medtronic, Abbott, Pfizer, Bayer, Saja, and Boehringer Ingelheim. SAK has received honoraria for consultancy for Medtronic, Bayer, Pfizer and Saja. OF has received honoraria for consultancy for Medtronic. None of the above interests are related to this article. All other authors declare no competing interests.

Data sharing

Individual participant data will be made available on request, directed to the corresponding author (MEK). Requests will be assessed for scientific rigour before being granted. After

approval of a proposal, data will be anonymised and securely transferred. A data sharing agreement may be required.

Ethics Statement

This study was approved by the National Emirates Institutional Review Board for COVID research (DOH/CVDC/2020/831) and was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The requirement for informed consent was waived for this retrospective analysis.

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Figure legends

Figure 1: Flowchart of study participants included in the analysis

Figure 2: Changes in QTc interval in patients treated with HY (with or without AZ). Panels (a) and (b) show baseline and peak QTc interval using Bazett and Fridericia formulas, respectively. Panels (c) and (d) show distribution of patients stratified by degree of QTc change using Bazett and Fridericia formulas, respectively.

Figure 3: Baseline and daily QTc interval change in patients treated with HY (with or without AZ) using (a) Bazett and (b) Fridericia formulas, respectively.

Figure 4: Baseline and maximal QTc measurements in patients treated with HY alone or in association with AZ using (a) Bazett and (b) Fridericia formulas, respectively.

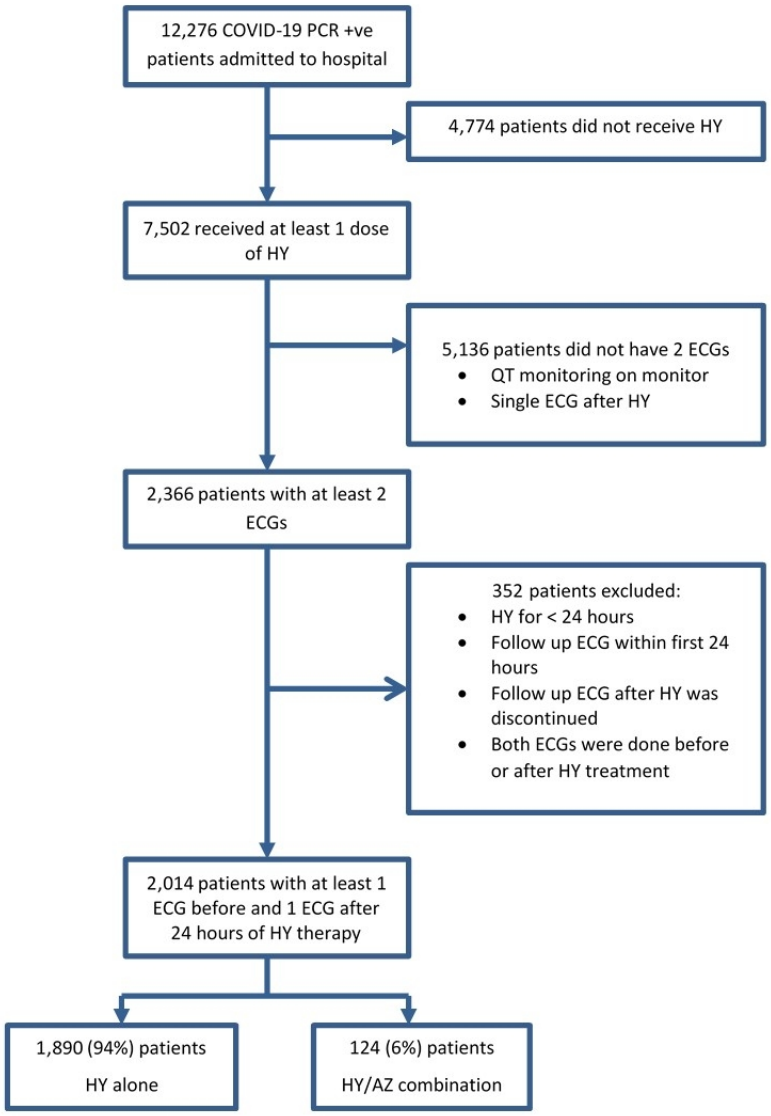
Figure 5: Relationship between QTc and mortality and disease severity. Panels (a) and (b) display maximal QTc interval in survivors and deceased patients (Bazett and Fridericia formulas, respectively). Distribution of maximal QTc intervals stratified by clinical severity of COVID-19 infection is shown in panels (c) and (d) using Bazett and Fridericia formulas, respectively.

Table 1: Baseline characteristics, risk factors and clinical course of patients

Baseline Characteristics and Clinical Course				
	Total 2,014 (100%)	HY only 1,890 (94%)	HY/AZ 124 (6%)	P value †
Baseline Characteristics				
Age, Mean (±SD)	46.8 (±12.6)	47.0 (±12.6)	43.8 (±12.2)	0.005
Male Sex, n (%)	1,727 (85.7%)	1,619 (85.6%)	108 (87.1%)	0.756
Ethnicity, n (%)				
• African	15 (0.7%)	15 (0.8%)	0 (0.0%)	0.686
• Arab	367 (18.2%)	342 (18.1%)	25 (20.3%)	
• Asian	1,612 (80.2%)	1,515 (80.3%)	97 (78.3%)	
• Caucasian	11 (0.5%)	10 (0.5%)	1 (0.8%)	
• Other	7 (0.4%)	6 (0.3%)	1 (0.8%)	
Length of Stay (days), Mean (±SD)	9.4 (±8.6)	9.0 (±8.3)	15.2 (±10.7)	<0.001
Length of HY treatment (Days), Mean (±SD)	6.4 (±2.3)	6.3 (±2.3)	7.6 (±2.7)	<0.001
Clinical Risk Factors				
BMI, Mean (±SD)	27.6 (±5.0)	27.7 (±5.1)	26.4 (±4.6)	0.003
BMI Categories, n (%)				
• < 25	593 (33.3%)	549 (32.9%)	44 (39.3%)	0.057
• 25-30	711 (39.9%)	662 (39.7%)	49 (43.7%)	
• 30-40	425 (23.9%)	406 (24.3%)	19 (17.0%)	
• > 40	51 (2.9%)	51 (3.1%)	0 (0.0%)	
Smoking Status, n (%)				
• Current smoker	109 (5.4%)	107 (5.7%)	2 (1.6%)	0.028
• Former smoker	74 (3.7%)	73 (3.9%)	1 (0.8%)	
• Non smoker	1,831 (90.9%)	1,710 (90.4%)	121 (97.6%)	
Diabetes, n (%)	736 (36.5%)	695 (36.8%)	41 (33.1%)	0.463
Hypertension, n (%)	786 (39.0%)	749 (39.6%)	37 (29.8%)	0.038
CKD, n (%)	141 (7.0%)	132 (6.9%)	9 (7.3%)	1.000
Cancer, n (%)	49 (2.5%)	45 (2.4%)	4 (3.2%)	0.771

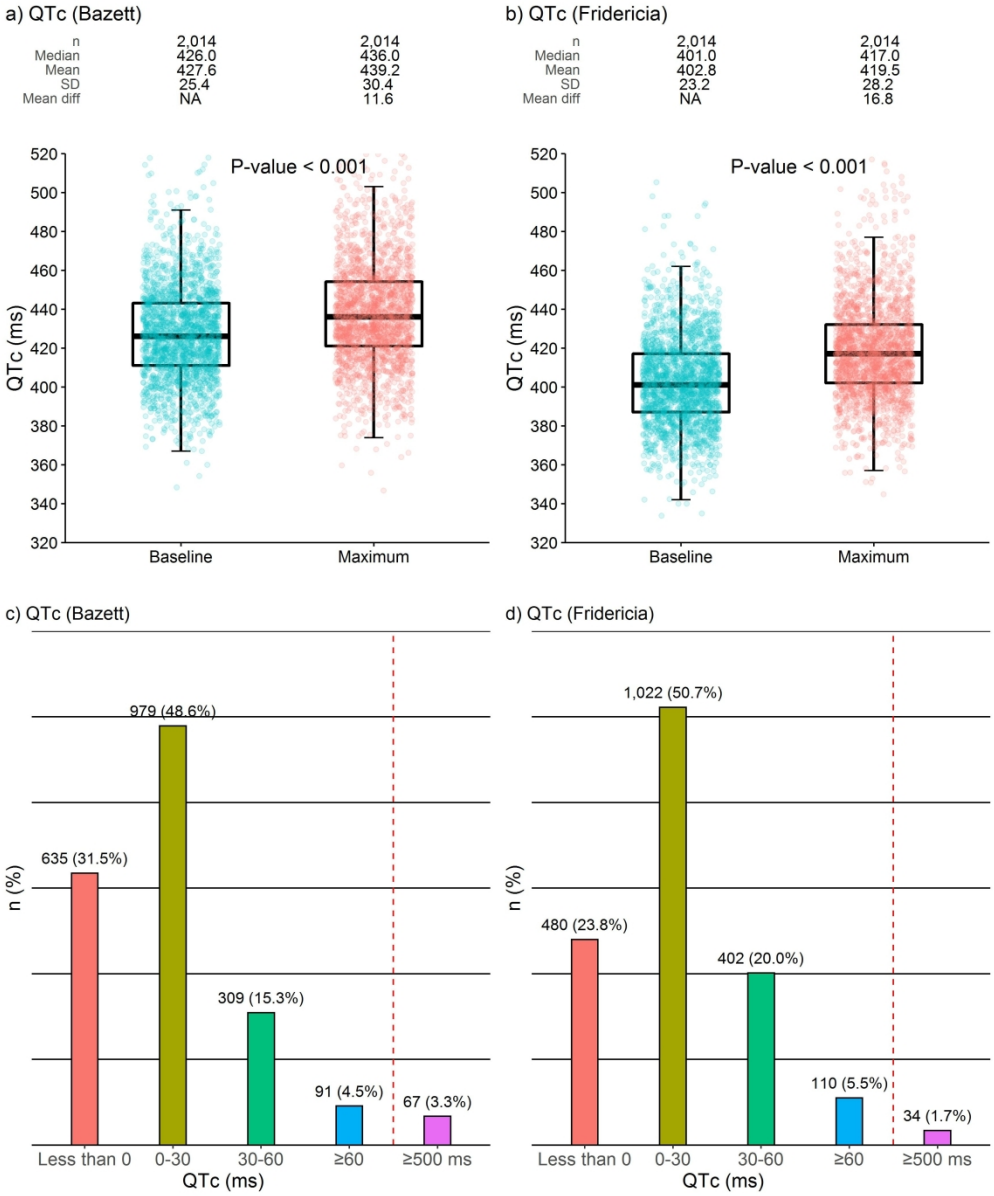
Lung disease, n (%)	118 (5.9%)	113 (6.0%)	5 (4.0%)	0.486
Structural heart disease, n (%)	155 (7.7%)	150 (7.9%)	5 (4.0%)	0.160
Liver disease, n (%)	15 (0.7%)	14 (0.7%)	1 (0.8%)	1.000
Immunosuppression, n (%)	49 (2.4%)	42 (2.2%)	7 (5.6%)	0.036
Clinical Course				
Clinical severity, n (%)				
• Asymptomatic	50 (2.5%)	46 (2.4%)	4 (3.2%)	<0.001
• Mild	772 (38.3%)	731 (38.7%)	41 (33.1%)	
• Moderate	736 (36.6%)	709 (37.5%)	27 (21.8%)	
• Severe	456 (22.6%)	404 (21.4%)	52 (41.9%)	
CXR findings, n (%)				
• Consolidation	1,390 (69.0%)	1,294 (68.5%)	96 (77.4%)	0.031
• No consolidation	251 (12.5%)	235 (12.4%)	16 (12.9%)	
• CXR not performed	373 (18.5%)	361 (19.1%)	12 (9.7%)	
Lung CT findings, n (%)				
• Normal	80 (4.0%)	73 (3.7%)	7 (5.6%)	<0.001
• Mild changes	523 (26.0%)	496 (26.3%)	27 (21.8%)	
• Moderate changes	785 (39.0%)	758 (40.2%)	27 (21.8%)	
• Severe changes	209 (10.3%)	192 (10.2%)	17 (13.7%)	
• Lung CT not performed	417 (20.7%)	371 (19.6%)	46 (37.1%)	
ICU admission, n (%)	241 (11.2%)	209 (11.1%)	32 (25.8%)	<0.001
Mechanical ventilation, n (%)	190 (9.4%)	166 (8.8%)	24 (19.3%)	<0.001
Inotropes, n (%)	183 (9.0%)	160 (8.4%)	23 (18.5%)	<0.001
Dialysis, n (%)	90 (4.5%)	82 (4.3%)	8 (6.4%)	0.379
Mortality, n (%)	80 (3.97%)	73 (3.86%)	7 (5.65%)	0.455

† Continuous variables were summarized using the t-test, while discrete variables were summarized using the Chi-square test.



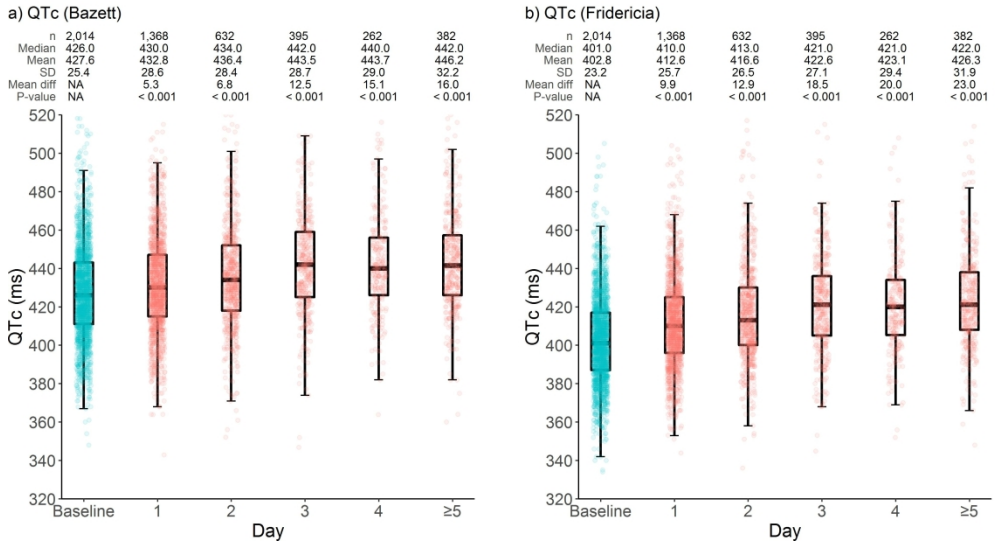
Flowchart of study participants included in the analysis

132x190mm (150 x 150 DPI)



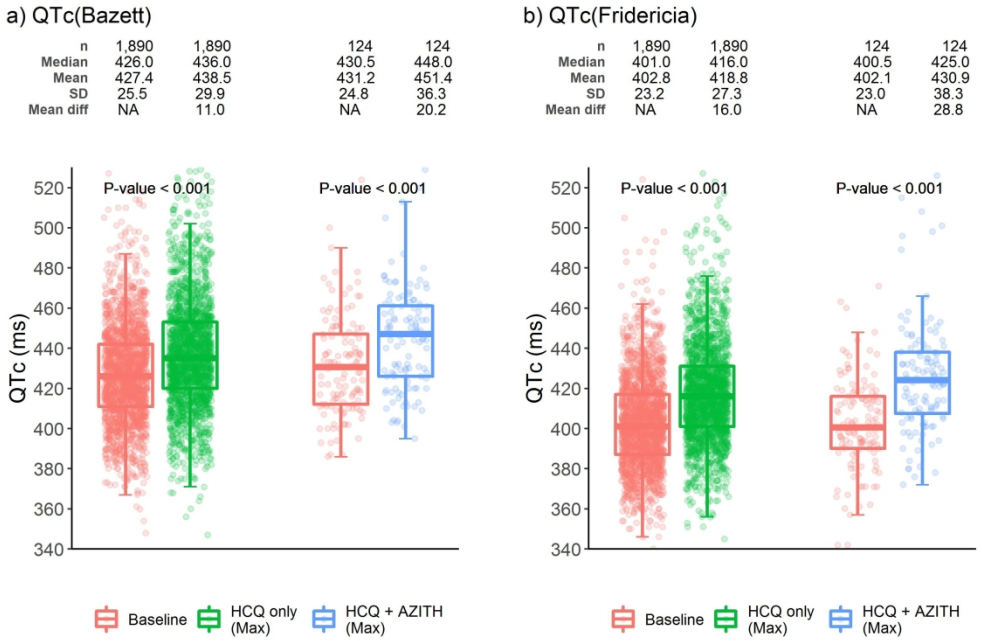
Changes in QTc interval in patients treated with HY (with or without AZ). Panels (a) and (b) show baseline and peak QTc interval using Bazett and Fridericia formulas, respectively. Panels (c) and (d) show distribution of patients stratified by degree of QTc change using Bazett and Fridericia formulas, respectively.

254x304mm (350 x 350 DPI)



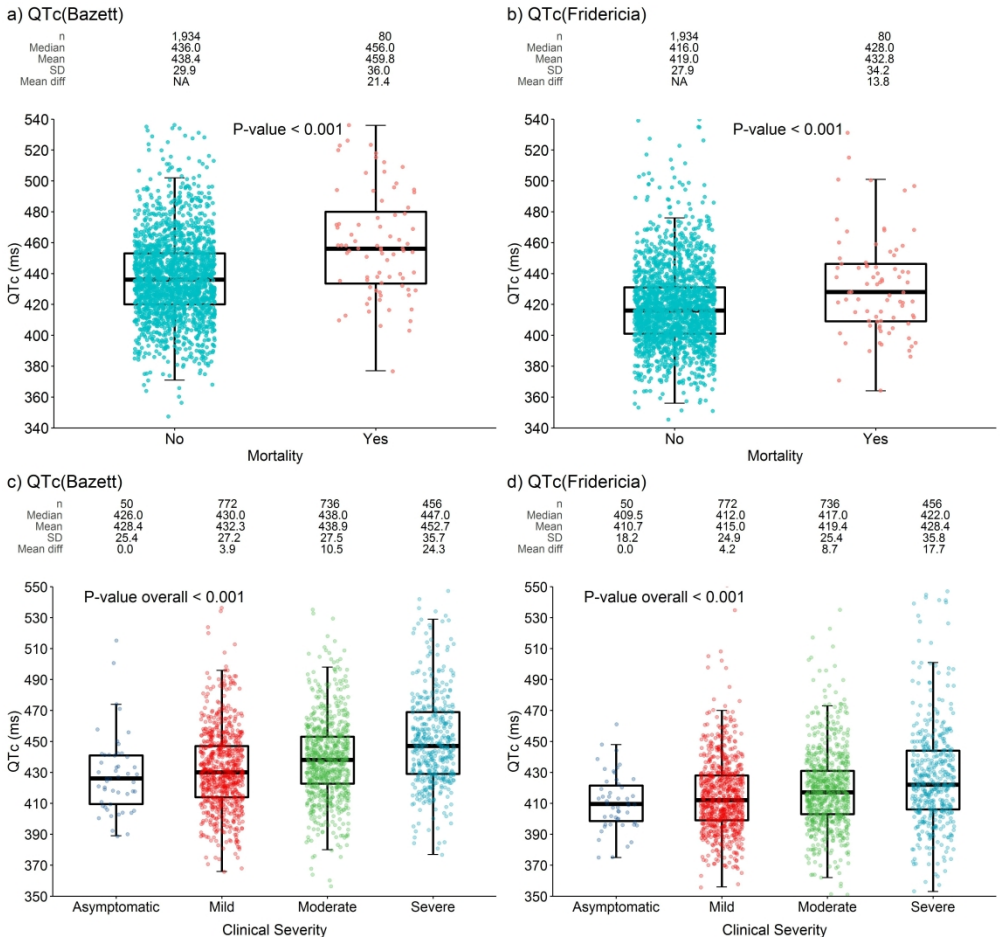
Baseline and daily QTc interval change in patients treated with HY (with or without AZ) using (a) Bazett and (b) Fridericia formulas, respectively.

304x165mm (350 x 350 DPI)



Baseline and maximal QTc measurements in patients treated with HY alone or in association with AZ using (a) Bazett and (b) Fridericia formulas, respectively.

228x152mm (350 x 350 DPI)



Relationship between QTc and mortality and disease severity. Panels (a) and (b) display maximal QTc interval in survivors and deceased patients (Bazett and Fridericia formulas, respectively). Distribution of maximal QTc intervals stratified by clinical severity of COVID-19 infection is shown in panels (c) and (d) using Bazett and Fridericia formulas, respectively.

381x355mm (350 x 350 DPI)

Supplementary Table 1: Multiple linear regression showing the association between $QTc_{(Bazett)}$ and mortality, adjusting for age, BMI, gender and comorbidity

Characteristic	Beta	95% CI	p-value
Intercept	425	416, 433	<0.001
Mortality (Ref: Alive)	20	13, 27	<0.001
Age	0.05	-0.07, 0.16	0.4
BMI	0.20	-0.06, 0.47	0.14
Gender (Ref: Male)	9.1	5.2, 13	<0.001
Comorbidity (Ref: No)	8.3	5.4, 11	<0.001

Supplementary Table 2: Multiple linear regression showing the association between $QTc_{(Fridericia)}$ and mortality, adjusting for age, BMI, gender and comorbidity

Characteristic	Beta	95% CI	p-value
Intercept	409	401, 417	<0.001
Mortality (Ref: Alive)	12	5.3, 18	<0.001
Age	0.16	0.06, 0.27	0.003
BMI	-0.08	-0.33, 0.17	0.5
Gender (Ref: Male)	8.3	4.7, 12	<0.001
Comorbidity (Ref: No)	5.7	3.0, 8.4	<0.001

Supplementary Table 3: Multiple linear regression showing the association between $QTc_{(Bazett)}$ and severity of COVID-19, adjusting for age, BMI, gender and comorbidity

Characteristic	Beta	95% CI	p-value
Intercept	424	412, 435	<0.001
Severity			
Asymptomatic (Ref)	—	—	
Mild	3.0	-5.5, 11	0.5
Moderate	9.2	0.61, 18	0.036
Severe	23	14, 32	<0.001
age	0.00	-0.11, 0.11	> 0.9
BMI	0.02	-0.24, 0.29	0.9
Gender (Ref: Male)	11	6.9, 14	<0.001
Comorbidity (Ref: No)	7.0	4.2, 9.9	<0.001

Supplementary Table 4: Multiple linear regression showing the association between $QTc_{(Fridericia)}$ and severity of COVID-19, adjusting for age, BMI, gender and comorbidity

Characteristic	Beta	95% CI	p-value
Intercept	407	396, 418	<0.001
Severity			
Asymptomatic (Ref)	—	—	
Mild	3.5	-4.6, 12	0.4
Moderate	7.3	-0.86, 15	0.080
Severe	16	7.8, 24	<0.001
age	0.13	0.02, 0.24	0.016
BMI	-0.20	-0.45, 0.05	0.12
Gender (Ref: Male)	9.3	5.7, 13	<0.001
Comorbidity (Ref: No)	4.9	2.2, 7.6	<0.001

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6*
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	6-7
		(*d*) If applicable, explain how loss to follow-up was addressed	6-7
		(*e*) Describe any sensitivity analyses	NA
Results			NA

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	8-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.